

Overview

Useful For

Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of Marfan syndrome, Loeys-Dietz syndrome, thoracic aortic aneurysm and dissections, or a related disorder

Second-tier testing for patients in whom previous targeted gene variant analyses for specific Marfan and related genes were negative

Establishing a diagnosis of a Marfan or a related disorder in some cases, allowing for appropriate management and surveillance for aneurysms and other disease features based on the gene involved

Identifying variants within genes known to be associated with increased risk for aneurysms and other disease features allowing for predictive testing of at-risk family members

Genetics Test Information

This test includes next-generation sequencing and supplemental Sanger sequencing to evaluate for variants in the *ACTA2*, *CBS*, *COL3A1*, *COL5A1*, *COL5A2*, *FBN1*, *FBN2*, *FLNA*, *MFAP5*, *MYH11*, *MYLK*, *NOTCH1*, *PRKG1*, *SKI*, *SLC2A10*, *SMAD3*, *SMAD4*, *TGFB2*, *TGFB3*, *TGFBR1*, and *TGFBR2* genes. Additionally, NGS is used to test for the presence of large deletions and duplications in a subset of genes.

This test may aid in the diagnosis of Marfan syndrome, Loeys-Dietz syndrome, familial thoracic aortic aneurysm and dissection (TAAD), or a related disorder.

Identification of a pathogenic variant may assist with prognosis, clinical management, familial screening, and genetic counseling.

[Prior Authorization](#) is available for this assay; see Special Instructions.

Highlights

This test uses next-generation sequencing with copy number variation analysis to test for variants in the *ACTA2*, *CBS*, *COL3A1*, *COL5A1*, *COL5A2*, *FBN1*, *FBN2*, *FLNA*, *MFAP5*, *MYH11*, *MYLK*, *NOTCH1*, *PRKG1*, *SKI*, *SLC2A10*, *SMAD3*, *SMAD4*, *TGFB2*, *TGFB3*, *TGFBR1*, and *TGFBR2* genes.

Special Instructions

- [Informed Consent for Genetic Testing](#)
- [Marfan and Related Disorders Patient Information](#)
- [Marfan Syndrome and Related Disorders Multi-Gene Panel Prior Authorization Ordering Instructions](#)
- [Informed Consent for Genetic Testing \(Spanish\)](#)

Method Name

Custom Sequence Capture and Targeted Next-Generation Sequencing followed by qPCR and/or Polymerase Chain Reaction (PCR) and Supplemental Sanger Sequencing

NY State Available

Yes

Specimen

Specimen Type

Varies

Ordering Guidance

[Targeted testing for familial variants \(also called site-specific or known mutation testing\)](#) is available for the genes on this panel. See [FMTT / Familial Mutation, Targeted Testing, Varies](#).

Shipping Instructions

Specimen preferred to arrive within 96 hours of collection.

Necessary Information

1. [Marfan and Related Disorders Patient Information](#) (T636) is strongly recommended, but not required, to be filled out and sent with the specimen. This information aids in providing a more thorough interpretation of test results. Ordering providers are strongly encouraged to complete the form and send it with the specimen.

2. Include physician name and phone number with specimen.

3. [Prior Authorization](#) is available for this test. **Submit the required form with the specimen.**

Specimen Required

Patient Preparation: A previous bone marrow transplant from an allogenic donor will interfere with testing. Call 800-533-1710 for instructions for testing patients who have received a bone marrow transplant.

Submit only 1 of the following specimens:

Specimen Type: Whole blood

Container/Tube: Lavender top (EDTA)

Specimen Volume: 3 mL

Collection Instructions:

1. Invert several times to mix blood.

2. Send specimen in original tube.

Specimen Stability Information: Ambient (preferred) 4 days/Refrigerated 14 days

Specimen Type: Extracted DNA

Container/Tube: 2 mL screw top tube

Specimen Volume: 100mcL (microliters)

Collection Instructions:

1. The preferred volume is 100 mcL at a concentration of 250 ng/mcL.

2. Include concentration and volume on tube.

Specimen Stability Information: Frozen (preferred)/Ambient/Refrigerated

Forms

1. **New York Clients-Informed consent is required.** Document on the request form or electronic order that a copy is on file. The following documents are available in Special Instructions:

-[Informed Consent for Genetic Testing](#) (T576)

-[Informed Consent for Genetic Testing-Spanish](#) (T826)

2. [Marfan and Related Disorders Patient Information](#) (T636) in Special Instructions

3. [Marfan Syndrome and Related Disorders Multi-Gene Panel Prior Authorization Ordering Instructions](#) in Special Instructions

4. If not ordering electronically, complete, print, and send a [Cardiovascular Test Request Form](#) (T724) with the specimen.

Specimen Minimum Volume

1 mL

Reject Due To

All specimens will be evaluated at Mayo Clinic Laboratories for test suitability.

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Varies		

Clinical and Interpretive

Clinical Information

Marfan syndrome (MFS) is an autosomal dominant genetic disorder affecting the connective tissue that occurs in approximately 1 to 2 per 10,000 individuals. It is characterized by the presence of skeletal, ocular, and cardiovascular manifestations and is caused by variants in the *FBN1* gene. Skeletal findings may include tall stature, chest wall deformity, scoliosis, and joint hypermobility. Lens dislocation (ectopia lentis) is the cardinal ocular feature, and mitral valve prolapse and aortic root dilatation/dissection are the main cardiovascular features. Diagnosis is based on the revised Ghent nosology and genetic testing of *FBN1*. Management aims to monitor and slow the rate of aortic root dilatation and initiate appropriate medical and/or surgical intervention as needed. Other phenotypes associated with the *FBN1* gene include autosomal dominant ectopia lentis (displacement of the lens of the eye), thoracic aortic aneurysm and dissections (TAAD), isolated skeletal features of MFS, MASS phenotype (mitral valve prolapse, aortic diameter increased, stretch marks, skeletal features of MFS), Shprintzen-Goldberg syndrome (Marfanoid-craniosynostosis; premature ossification and closure of sutures of the skull), and autosomal dominant Weill-Marchesani syndrome (short stature, short fingers, ectopia lentis).

Loeys-Dietz syndrome (LDS) is an autosomal dominant connective tissue disease with significant overlap with Marfan syndrome but may include involvement of other organ systems and is primarily caused by variants in *TGFBR1* and *TGFBR2*. Features of LDS that are not typical of MFS include craniofacial and neurodevelopmental abnormalities, and arterial tortuosity with increased risk for aneurysm and dissection throughout the arterial tree. Variants of the *SMAD3* gene have been reported in families with an LDS-like phenotype with arterial aneurysms and tortuosity and early onset osteoarthritis. Variants of the *TGFB3* gene have also been reported in families with an LDS-like phenotype, although these individuals tended to not have arterial tortuosity.

TAAD is a genetic condition primarily involving dilatation and dissection of the thoracic aorta but may also include aneurysm and dissection of other arteries. TAAD has a highly variable age of onset and presentation and may involve additional features such as congenital heart defects and other features of connective tissue disease or smooth muscle abnormalities depending on the causative gene. The gene most commonly involved in familial TAAD is *ACTA2*. For other genes also implicated in TAAD, refer to the table below.

The *COL3A1* gene causes Ehlers Danlos syndrome, vascular type (type IV), an autosomal dominant connective tissue disease with characteristic facial features, thin, translucent skin, easy bruising, and arterial, intestinal, and uterine fragility. Arterial rupture may be preceded by aneurysm or dissection or may occur spontaneously. The *COL5A1* and *COL5A2* genes cause Ehlers Danlos syndrome, classic type (type I and type II), an autosomal dominant connective tissue disorder characterized by skin hyperextensibility, widened atrophic scars, joint hypermobility, smooth, velvety skin, and easy bruising. The *FLNA* gene causes *FLNA*-related periventricular nodular heterotopia (PVNH), an X-linked neuronal migration disorder where the majority of affected individuals are female. This condition is characterized by seizures, hyperflexible joints, and cardiac findings, which include thoracic aortic aneurysm and dissection. Some individuals show clinical overlap with EDS.

Autosomal dominant variants of the *FBN2* gene are known to cause congenital contractural arachnodactyly (CCA), which has several overlapping features with Marfan syndrome, including dolichostenomelia, scoliosis, pectus deformity, arachnodactyly, and a risk for thoracic aortic aneurysm.

Variants of the *CBS* gene cause homocystinuria an autosomal recessive disorder of amino acid metabolism with clinical overlap with Marfan syndrome; including lens dislocation and skeletal abnormalities, as well as increased risk for abnormal blood clotting.

Variants in the *SKI* gene cause Shprintzen-Goldberg syndrome (SGS), an autosomal dominant condition with overlap with LDS and MFS. Distinguishing features of SGS include hypotonia and intellectual disability. Aortic root dilatation is less frequent in SGS than in LDS or MFS, but, when present, it can be severe.

Homozygous and compound heterozygous loss of function variants in the *SLC2A10* gene have been described in arterial tortuosity syndrome, a condition characterized by generalized tortuosity and elongation of all major arteries in addition to other connective tissue disease features.

Variants in the *NOTCH1* gene cause aortic valve disease, with individuals displaying a range of aortic valve abnormalities and severe valve calcification.

Genes included in Marfan Syndrome and Related Disorders Multi-Gene Panel:

Gene	Protein	Inheritance	Known association
<i>ACTA2</i>	Actin, alpha-2, smooth muscle, aorta	AD	TAAD
<i>CBS</i>	Cystathionine beta-synthase	AR	Homocystinuria



<i>COL3A1</i>	Collagen, type III, alpha-1	AD	Ehlers-Danlos syndrome, vascular type (EDS type IV)
<i>COL5A1</i>	Collagen, type V alpha-1	AD	Ehlers-Danlos Syndrome, Classic Type (EDS type I, EDS type II)
<i>COL5A2</i>	Collagen, type V alpha-2	AD	Ehlers-Danlos Syndrome, Classic Type (EDS type I, EDS type II)
<i>FBN1</i>	Fibrillin 1	AD	Marfan syndrome/TAAD/Ectopia Lentis/ MASS phenotype/Sh printzen-Goldberg syndrome/Weill-Marchesani syndrome
<i>FBN2</i>	Fibrillin 2	AD	Congenital Contractural Arachnodactyly
<i>FLNA</i>	Filamin A	X-linked	Ehlers-Danlos syndrome and periventricular nodular heterotopia/X-linked cardiac valvular dysplasia/ otopalatodigital spectrum disorders/TAAD
<i>MFAP5</i>	Microfibril-associated protein 5	AD	TAAD
<i>MYH11</i>	Myosin, heavy chain 11, smooth muscle	AD	TAAD
<i>MYLK</i>	Myosin light chain kinase	AD	TAAD
<i>NOTCH1</i>	Notch, drosophila, homolog of, 1	AD	Aortic valve disease/Adams-Oliver Syndrome
<i>PRKG1</i>	Protein kinase, cGMP-dependent, type 1	AD	TAAD
<i>SKI</i>	V-SKI avian sarcoma viral oncogene homolog	AD	Shprintzen-Goldberg syndrome
<i>SLC2A10</i>	Solute carrier family 2 (facilitated glucose transporter), member 10	AR	Arterial Tortuosity syndrome/TAAD (Autosomal Recessive)
<i>SMAD3</i>	Mothers against decapentaplegic, drosophila, homolog of, 3	AD	Loeys-Dietz syndrome/TAAD
<i>SMAD4</i>	Mothers against decapentaplegic, drosophila, homolog of, 4	AD	TAAD/JPS/JPS-HHT
<i>TGFB2</i>	Transforming growth factor, beta-2	AD	TAAD

<i>TGFB3</i>	Transforming growth factor, beta-3	AD	Loeys-Dietz syndrome (Rienhoff syndrome)/TAAD
<i>TGFBR1</i>	Transforming growth factor-beta receptor, type I	AD	Loeys-Dietz syndrome/TAAD
<i>TGFBR2</i>	Transforming growth factor-beta receptor, type II	AD	Loeys-Dietz syndrome/TAAD

Abbreviations: Autosomal dominant (AD), autosomal recessive (AR); thoracic aortic aneurysm and dissection (TAAD); juvenile polyposis syndrome (JPS); juvenile polyposis syndrome-hereditary hemorrhagic telangiectasia (JPS-HHT)

Indications for testing include but are not limited to:

- Patients who meet clinical diagnostic criteria (Revised Ghent nosology) for Marfan syndrome
- Patients in whom no specific Marfan or related disorder is evident but for whom there is a clear familial component
- Patients whose family history is consistent with TAAD
- Patients with a personal or family history of thoracic aortic aneurysm and/or dissection or a personal or family history of multiple arterial aneurysms

Reference Values

An interpretive report will be provided.

Interpretation

Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Cautions

Clinical Correlations:

Some individuals who have involvement of 1 or more of the genes on the panel may have a variant that is not identified by the methods performed (eg, promoter variants, deep intronic variants). The absence of a variant, therefore, does not eliminate the possibility of Marfan syndrome or a related disorder.

Test results should be interpreted in context of clinical findings, family history, and other laboratory data. Misinterpretation of results may occur if the information provided is inaccurate or incomplete. If testing was performed because of a family history of Marfan syndrome or a related disorder, it is often useful to first test an affected family member. Identification of a pathogenic variant in an affected individual would allow for more informative testing of at-risk individuals.

Technical Limitations:

Next-generation sequencing may not detect all types of genetic variants. Additionally, rare alterations (ie, polymorphisms) may be present that could lead to false negative or positive results. If results do not match clinical findings, consider alternative methods for analyzing these genes, such as Sanger sequencing or large deletion/duplication analysis. If the patient has had an allogeneic blood or marrow transplant or a recent (ie, <6 weeks from time of sample collection) heterologous blood transfusion these results may be inaccurate due to the presence of donor DNA.

Reclassification of Variants Policy:

At this time, it is not standard practice for the laboratory to systematically review likely pathogenic variants or variants of uncertain significance that are detected and reported. The laboratory encourages health care providers to contact the laboratory at any time to learn how the status of a particular variant may have changed over time.

Contact the laboratory if additional information is required regarding the transcript and/or human genome assembly used for the analysis of this patient's results.

Clinical Reference

1. Loeys BL, Dietz HC, Braverman AC, et al: The revised Ghent nosology for the Marfan syndrome. *J Med Genet.* 2010 Jul;47(7):476-485
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3. Loeys BL, Chen J, Neptune ER, et al: A syndrome of altered cardiovascular, craniofacial, neurocognitive and skeletal development caused by mutations in *TGFBR1* or *TGFBR2*. *Nat Genet.* 2005 Mar;37(3):275-281
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12. van de Laar IMBH, van der Linde D, Oei EHG, et al: Phenotypic spectrum of the SMAD3-related aneurysms-osteoarthritis syndrome. *J Med Genet.* 2012 Jan;49(1):47-57
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15. Malfait F, Wenstrup R, Paepe AD: Classic Ehlers-Danlos syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. *GeneReviews* [Internet]. University of Washington, Seattle; 2007. Updated July 26, 2018. Accessed September 22, 2021. Available at www.ncbi.nlm.nih.gov/books/NBK1244/
16. Online Mendelian Inheritance in Man. Available at www.ncbi.nlm.nih.gov/sites/entrez?db=OMIM

Performance

Method Description

Next-generation sequencing (NGS) is performed using an Illumina instrument with paired-end reads. The DNA is prepared for NGS using a custom Agilent SureSelect Target Enrichment System. Data is analyzed with a bioinformatics software pipeline for sequence variants and the presence of large intragenic deletions and duplications. Supplemental Sanger sequencing or qPCR may be performed occasionally in regions where NGS is insufficient for data capture or not specific enough to correctly identify a variant. Sanger sequencing or qPCR may also be used for confirmatory testing. (Unpublished Mayo method)

Genes analyzed: *ACTA2*, *CBS*, *COL3A1*, *COL5A1*, *COL5A2*, *FBN1*, *FBN2*, *FLNA*, *MFAP5*, *MYH11*, *MYLK*, *NOTCH1*, *SKI*, *SLC2A10*, *SMAD3*, *SMAD4*, *TGFB2*, *TGFB3*, *TGFBR1*, and *TGFBR2*.

PDF Report

No

Day(s) Performed

Monday

Report Available

2 to 4 weeks after prior authorization approved

Specimen Retention Time

Extracted DNA: 2 months

Performing Laboratory Location

Rochester

Fees and Codes

Fees

- Authorized users can sign in to [Test Prices](#) for detailed fee information.
- Clients without access to Test Prices can contact [Customer Service](#) 24 hours a day, seven days a week.
- Prospective clients should contact their Regional Manager. For assistance, contact [Customer Service](#).

Test Classification

This test was developed, and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information

81410

LOINC® Information

Test ID	Test Order Name	Order LOINC Value
MFRGP	Marfan and Related Genetic Panel	In Process

Result ID	Test Result Name	Result LOINC Value
36650	Gene(s) Evaluated	48018-6
36651	Result Summary	50397-9
36657	Result Details	82939-0
36658	Interpretation	69047-9
36962	Additional Information	48767-8
36963	Method	85069-3
36964	Disclaimer	62364-5
36692	Reviewed by	18771-6

Prior Authorization

Insurance preauthorization is available for this testing; forms are available in Special Instructions.

Patient financial assistance may be available to those who qualify. Patients who receive a bill from Mayo Clinic Laboratories will receive information on eligibility and how to apply.